Autonomic Dysfunction in Hypersomnia

Current Sleep Medicine Reports
Section. Hypersomnia. Article Type: Review

Title: Autonomic Dysfunction in Hypersomnia

Authors:
Alessandro Silvani, MD, PhD [1], Isabelle Lambert, MD, PhD [2], Anna Heidbreder, MD [3], Yves Dauvilliers, MD, PhD [4], Lucie Barateau, MD, PhD [4]
Affiliations:
[1] Department of Biomedical and Neuromotor Sciences, University of Bologna, Ravenna Campus, Ravenna, Italy
[2] APHM, Timone hospital, Sleep Unit, Epileptology and Cerebral Rhythmology, and Aix Marseille Univ, Inserm, INS, Inst Neurosci Syst, Marseille, France
[3] Medical University Innsbruck, Department of Neurology, Sleep Disorders Unit, Innsbruck Austria
[4] National Reference Center for Narcolepsy and Rare Hypersomnias, Department of Neurology, Gui-de-Chauliac University Hospital; and Institute for Neurosciences of Montpellier (INM), INSERM, Université de Montpellier, France

Corresponding author : Lucie Barateau, Service de Neurologie, Gui-de-Chauliac Hospital, CHU Montpellier, 80 avenue Augustin Fliche, 34295 Montpellier Cedex 5, France. Tel: +33 4 67 33 72 77. E-mail: lucie.barateau@yahoo.fr

Number of words: 3458

Number of words in the abstract: 174

Number of references: 92

Number of figures: 1 ; Number of tables: 0

Abstract

Purpose of review. This article provides a comprehensive overview of the literature on autonomic dysfunctions in central disorders of hypersomnolence: narcolepsy type 1 and type 2, idiopathic hypersomnia, and Kleine Levin syndrome. Clinical implications are discussed.

Recent Findings. The interactions between the autonomic nervous system and central disorders of hypersomnolence are complex. Patients affected with these rare sleep diseases often report autonomic symptoms. Recent studies systematically assessed these symptoms in large cohorts of well-characterized patients, and some studies objectified autonomic disturbances during wakefulness and sleep, mostly with indirect measures.

Summary. Autonomic impairment is frequent in central disorders of hypersomnolence, and the pathophysiological mechanisms underlying this dysfunction are not yet fully elucidated. In

narcolepsy type 1, the deficiency in orexin/hypocretin neurons could play a role, and that has been confirmed in animal models of the disease. Management of central disorders of hypersomnolence is nowadays only symptomatic, with wake-promoting agents, often psychostimulants. Further research is needed to understand the consequences of these medications on the autonomic nervous system, and their possible relation to long-term cardiovascular risk.

Keywords: Hypersomnia, sleepiness, autonomic dysfunction, narcolepsy, idiopathic hypersomnia, Kleine Levin syndrome, blood pressure

Introduction

Animal and human studies have shown that disorders of the autonomic nervous system may influence sleep physiology, and that sleep disorders may be associated with autonomic dysfunctions. However, in central disorders of hypersomnolence (CDH), the causal link with autonomic dysfunction and its possible impact on health remain unsettled [1]. Among CDH, the current International Classification of Sleep Disorders (ICSD-3) [2] distinguishes narcolepsy type 1 (NT1) (formerly named narcolepsy with cataplexy) and type 2 (NT2) (without cataplexy), idiopathic hypersomnia (IH), and Kleine-Levin syndrome (KLS) [3]. Excessive daytime sleepiness (EDS) is the main and often most disabling symptom of these rare sleep disorders, defined in ICSD-3 by "daily episodes of an irrepressible need to sleep or daytime lapses into sleep". However, EDS can also be accompanied by an increased need for sleep, and by sleep inertia upon awakening, especially in IH. A recent position paper from European experts proposed to define "hypersomnolence" as "the presence of EDS and/or excessive need of sleep or an increased quantity of sleep" [4], and hypersomnia would be the "objectified complaint of excessive need of sleep". In this review, we provide an overview of the literature to describe autonomic dysfunctions in NT1, NT2, IH, and KLS. Autonomic impairment and objective disturbances are reported during both wakefulness and sleep. The clinical implications and perspective for future research are also discussed. Current treatments of these disorders, especially wake-promoting agents and psychostimulants may have undesirable cardiovascular side effects.

Narcolepsy

NT1 is a "model disease" of hypersomnolence, but patients have also other symptoms. Cataplexy, i.e. sudden loss of muscle tone triggered by positive emotions, is pathognomonic of the disease. Disrupted nocturnal sleep (DNS) is the third most common symptom [5, 6], and sleep paralysis and hypnagogic/hypnopompic hallucinations are also typically reported [7, 8]. NT1 has a unique pathophysiology. It is due to the deficiency of orexins (ORX)/ hypocretins (orexin A and B, also named hypocretin 1 and 2, respectively), which are neuropeptides synthesized by neurons of the hypothalamus. Orexin deficiency in NT1 can be confirmed with the measurement of low levels of ORX (<110 pg/ml) in the cerebrospinal fluid (CSF). Although they represent a restricted group of cells, ORX neurons project widely through the brain, including to brain structures involved in wake and sleep regulation [9]. ORX play an important

role in sleep and wake regulation, but also in many other functions, such as energy metabolism, motivation, reward, addiction, and stress [10]. Their modulating effects on the autonomic nervous system is well-established and has also been well studied in animal models of the disease [11, 12]. Narcolepsy management is nowadays only symptomatic, and most medications used (namely psychostimulants, sodium oxybate, and antidepressant agents to manage cataplexy) may also interfere with autonomic and cardiovascular system functioning [13].

Clinical autonomic disturbances

Autonomic symptoms and signs have been reported for decades in narcolepsy [14]: fainting spells, erectile dysfunction, pupillary abnormalities, night sweats, gastric or digestive problems, hypotension, dry mouth, heart palpitations, and disturbed skin temperature profiles. More recently, these symptoms were systematically assessed in a large sample of well-characterized NT1 patients, using the SCOPA-AUT self-questionnaire, a tool previously validated in Parkinson's disease [15]. A large spectrum of clinical autonomic disturbances was found, with impairment in the six domains of the scale: gastrointestinal, urinary, cardiovascular, thermoregulatory, pupillomotor and sexual. These disturbances were associated with older age, poorer quality of life, and more depressive symptoms. The surprising absence of effect of drugs intake for narcolepsy suggested that dysautonomia could be more a trait than a state in NT1 [15].

Objective autonomic dysfunction

In NT1, several authors measured of dysautonomia objectively, but often with indirect techniques. These studies have yielded so far conflicting results regarding the direction of changes in sympathetic activity in comparison with control subjects [16]. The heterogeneity of the study samples in terms of age, gender, treatment status (drug-naïve or withdrawal), and comorbidities, together with the relatively small sample sizes could prevent the generalization of these findings.

A recent study on a small sample of 12 de-novo patients with NT1 compared to control subjects evaluated cardiovascular function by means of head-up tilt test, Valsalva maneuver, deep breathing, hand grip, and cold face, sudomotor function by means of *Sudoscan*, and autonomic symptoms by means of the SCOPA-AUT questionnaire [17]. The study reported alterations in tests of cardiac activity consistent with a blunted parasympathetic modulation

during wakefulness, mild sudomotor dysfunction, and a large variety of autonomic symptoms in NT1.

The blood pressure (BP) profile has been quite well-studied in narcolepsy. NT1 seems to be associated with a blunted fall of BP from wakefulness to sleep, and particularly to rapid-eye-movement (REM) sleep, and with a variable decrease in BP during wakefulness [18]. In line with data on ORX knock-out mice lacking only ORX peptides and on ORX-ataxin3 mice lacking the whole ORX neurons, a non-dipping BP profile was indeed reported in adult subjects with NT1 [19–21]. This condition in adults is associated with greater cardiovascular risk, and patients with narcolepsy seem to have increased cardiovascular morbidity [22]. However, further epidemiological studies are warranted to clarify the clinical importance of these findings [23]. Some studies in adults found a normal BP during wakefulness but a relative higher BP during sleep [24, 25], especially during REM sleep [20]. In a small sample, no association was found between residual ORX levels in the CSF and BP changes in NT1 [26], but a floor effect remains possible. Finally, the effect of medication for narcolepsy on BP seems important in the long term, with an increased diastolic BP and heart rate (HR) in patients treated by stimulants compared to drug-free patients [27].

Orexin neurons are an integral part of the central autonomic network, with the potential to drive bidirectional changes in parasympathetic activity to the heart and in sympathetic activity to the heart and blood vessels either directly or indirectly. Therefore, a deficit in the ORX signaling can induce HR alterations [28]. Several authors found similar HR mean values and similar HR in NT1 versus control subjects [19, 25, 29, 30], or sometimes subtle alterations of HR variability in patients with NT1 [29, 31–33] and in mouse models of NT1. However, a study showed lower HR during wakefulness in a young and drug-naïve sample of patients [34]. Higher HR in NT1, compared to controls, was found in other studies, particularly during sleep [20, 35, 36]. The HR responses to internal stimuli during sleep (arousals and legs movements) were found blunted in NT1 [35, 37], whereas those to emotional stimuli during wakefulness were found preserved [38]. An increased LF/HF ratio was also found, suggesting an increased sympathetic modulation [39], but later data called this interpretation into question [40].

The only direct measure of sympathetic activity is the recording of muscle sympathetic nerve activity (MSNA) by microneurography. Two studies, never replicated ever since, succeeded in recording MSNA in NT1. A low sympathetic tone during wakefulness was found

in a small sample of adult drug-naïve patients**,** and this reduction was associated with lower residual CSF ORX levels [34]. During sleep, MSNA recording is very challenging. One study showed a physiologic decrease in MSNA from wakefulness to NREM sleep, and an increase in REM sleep, with relative magnitude comparable to that in controls [25]. Similar results were obtained for the skin sympathetic activity (SSA), which was estimated by measuring changes in skin blood flow and skin potential [25]. Nevertheless, a pharmacological study on the ORX knock-out mouse model of NT1 concluded that a defect in the modulation of sympathetic activity to blood vessels was mainly responsible for the blunted sleep-related differences in BP occurring in this model [12]. This discrepancy may point to species differences or indicate a key role of the sympathetic control of other vascular districts, such as the splanchnic and the renal districts, in the sleep-related cardiovascular changes associated with NT1.

NT1 is often associated with other sleep abnormalities (sleep apnea, parasomnia, periodic legs movements (PLMS), REM sleep dysregulation, muscle overactivity during sleep), and with a wide range of comorbidities such as neuropsychiatric disorders, obesity, and metabolic disturbances. Some of these abnormalities and comorbidities could potentially explain, or at least exacerbate, autonomic dysfunction in this disease.

Obesity, a condition known to be associated with increased sympathetic activity [41], is very frequent in NT1, with up to one-third of adult patients obese, and half of children [42, 43]. This condition may be linked to ORX deficiency, but this is not yet fully understood. Weight gain usually occurs at the onset of the disease, especially in children, and often with precocious puberty [42, 44]. In a recent study, differences in plasma metabolic profiles between patients with NT1 and controls were identified. A targeted liquid chromatography-mass spectrometry metabolomics approach was used to measure more than one hundred circulating, low-molecular-weight metabolites in plasma samples from drug-free fasted subjects with NT1, and compared with data from control subjects matched for body mass index [45]. A study showed that rest energy expenditure, measured by indirect calorimetry, is decreased in NT1 [46], but other authors found no difference with respect to controls [32, 47]. It has been hypothesized that sympathetic tone reduction would explain the increased fat accumulation in narcolepsy, through a deficiency in catabolic processes [48]. However, the activity of brown adipose tissue measured by ^{123}-I-MIBG SPECT and ^{18}-F-FDG PET was not different between NT1 and controls [49]. Many patients with NT1 have sleep apnea syndrome, with a relatively high prevalence (around 25 to 30%) probably linked to obesity and overweigh [50]. This frequent

condition may lead to increased sympathetic tone and diminished baroreceptor sensitivity, thus increasing the risk of higher BP, non-dipping BP profile, and cardiovascular diseases.

Disrupted nocturnal sleep (DNS) has been less studied so far, but could be the third most common symptom in NT1 [6, 51], and this fragmented nocturnal sleep could also lead to an increased sympathetic drive. A study demonstrated that reduced ORX activity is associated with increased atherosclerosis burden in mouse models of NT1. Unexpectedly, mice subjected to sleep fragmentation in this study also produced less ORX, and developed larger atherosclerotic lesions [52]. In a recent study about the complaint of DNS in adult patients, DNS severity, assessed with one item of the validated Narcolepsy Severity Scale [53], was associated with higher autonomic dysfunction assessed by the SCOPA-AUT questionnaire [6]. Restless legs syndrome [54] and PLMS are frequent in NT1 [55, 56], and these conditions are also associated with an increased sympathetic activity. It is known that PLMS can induce transient rises in HR and BP, even more if they are associated with micro-arousals, but a weakening of this normal autonomic response to PLMS was shown in NT1 [37]. REM sleep behavior disorder (RBD), a parasomnia is also frequent in NT1, probably affecting two third of patients, even though its manifestations are different and typically less severe than those of the idiopathic form (iRBD), which has a distinct pathophysiology associated with alpha-synucleinopathies [57]. In iRBD, patients have cardiac sympathetic denervation and reduced HR variability during sleep. In RBD comorbid with NT1, however, cardiac scintigraphy revealed that ^{123}I-MIBG uptake was higher than in iRBD and comparable with controls [58]. Nevertheless, REM sleep without atonia seemed related to decreased cardiac sympathetic innervation in NT1 [59]. Urinary and plasma catecholamine levels measured over 24-hours were reported to be normal in narcolepsy [60], but the sample was small, CSF ORX was not measured, and the results have never been replicated. Abnormal pupillary reaction during darkness [61] and impaired nocturnal penile tumescence [62] have also been reported in patients with narcolepsy, further supporting the occurrence of autonomic alterations in these patients.

Childhood Narcolepsy type 1

Although the first symptoms of NT1 often occur in childhood or adolescence, children with NT1 have been understudied regarding autonomic dysfunction. The autonomic alterations associated with NT1 may vary across the lifespan, and future studies should focus on this population, even if research is more challenging because normative data are often lacking. A study compared 12 drug-naïve children with NT1 to 23 healthy children, and analyzed beat-to-

beat HR during nocturnal sleep, at baseline and after sodium oxybate. The authors found a slightly higher HR variability in all sleep stages in NT1 at baseline and a tendency to decreased HR variability in REM sleep under sodium oxybate [33]. In another study, 27 children and adolescents with NT1 (including 26 children with documented ORX deficiency), were compared to 19 children with sleepiness complaints but no objective sleep abnormalities [24]. During wakefulness and nocturnal sleep, pulse transit time (PTT) and HR were studied. The authors found a similar HR between groups, but a reduced lengthening of PTT during total sleep and REM sleep compared to nocturnal wakefulness in NT1. Since decreases in BP lead to lengthening of PTT, these results are fully consistent with the finding of smaller differences in BP between wakefulness and sleep, and particularly of REM sleep, in adult subjects with NT1. The finding of a non-dipper BP profile in adult patients with NT1 has also been recently confirmed in children and adolescents with NT1 [63]. Finally, a recent study explored orthostatic intolerance in a retrospective sample of 89 children with CDH, including mainly NT1, and found that one third of children exhibited this symptom at initial presentation, with female predominance, and the results were not significantly related to medication, sleepiness, or diagnostic category [64].

Narcolepsy type 2

Patients with NT2 have the same clinical picture as NT1, including EDS, sleep paralysis, hallucinations, and DNS, but without cataplexy, and with ORX levels above 110 pg/mL when CSF analysis is performed [7, 8]. However, the phenotype of NT2 is more and more subject to debate, with a lack of large samples in the literature [65]. This disorder may be more heterogeneous than generally believed, and may be related to IH in some patients, with some overlap between these conditions [66, 67]. Conversely, some patients with NT2 may later develop cataplexy and develop NT1, whereas other may relapse, and still others may persist into the NT2 phenotype [8]. Patients with NT2 are rarely studied as an individualized category, often compared to NT1. A decreased HR variability associated with micro-arousals and with PLMS was found in patients with narcolepsy (including NT2) compared with control subjects, but also in patients with vs. without ORX deficiency [35]. In a small retrospective study of HR variability, with few patients (11 NT1, 20 NT2, and 12 healthy controls), and without CSF ORX measurement, the authors found a higher LF/HF ratio in patients than in controls during NREM sleep, but also found evidence of lower parasympathetic modulation in NT1 than in NT2 during REM sleep [68].

Idiopathic Hypersomnia

IH is a rare disease, affecting often young females. Long and unrefreshing naps are typical in these patients [69], and their nocturnal sleep is prolonged and undisturbed, with sleep inertia sometimes severe when they wake up [3]. As in NT2, little is known about the underlying mechanisms in IH. Both are probably heterogeneous disorders, with no biological markers discovered so far, and a possible overlap between these conditions [70, 71]. There is a small body of literature regarding autonomic dysfunction in IH, and few reviews on the topic [72]. Nevertheless, it seems that symptoms of autonomic nervous system dysfunction are common, as first reported in a case series [73]. A study showed that patients with IH had more often cold extremities and fainting than controls [74], and another reported lower BP in IH than in narcolepsy, but without a healthy control group [75]. The HR variability assessment in IH patients versus controls revealed a dysfunction of the parasympathetic activity during wakefulness and sleep, and an altered autonomic response to arousals [76]; however patients were not diagnosed according to ICSD-3 criteria [77]. More recently, in a sample of 138 patients with IH and 81 controls, autonomic symptoms were evaluated with an online survey through the Composite Autonomic Symptom Score-31 (COMPASS-31) [78]. This questionnaire assesses autonomic functioning on 6 domains (secretomotor, vasomotor, pupillomotor, gastrointestinal, orthostatic intolerance, and urological). Patients had more autonomic symptoms in all domains, and this was associated with more sleepiness and worse quality of life. The mechanisms underlying autonomic dysfunction in IH are unknown, but it could be hypothesized that a lack of physical activity, due to hypersomnia, could induce deconditioning and, hence, orthostatic intolerance. A high prevalence of deconditioning, assessed as a reduced maximum oxygen uptake during exercise, has been associated with orthostatic intolerance in subjects without IH [79]. It is also conceivable that autonomic symptoms contribute to the global burden of disease in IH, and also to the fatigue experienced by many patients with IH, a qualitatively different symptom that often accompanies EDS and hypersomnia [4].

Kleine-Levin Syndrome

KLS is a periodic disorder of hypersomnolence, with relapsing-remitting episodes of hypersomnia, associated with behavioral, psychiatric, and cognitive disturbances, and sometimes with hyperphagia or hypersexuality [80]. Based on clinical experience, patients can also report some autonomic symptoms during an episode, but a systematic assessment of these

symptoms has not been reported to date. No reliable disease biomarker has been identified so far, and the pathophysiology of KLS remains mysterious. A recurrent primary hypothalamic dysfunction, of inflammatory or autoimmune origin, could underlie this syndrome, but this hypothesis relies on indirect findings and remains to be proven [81, 82]. Few CSF ORX measurements were reported in the literature in these patients, with the frequent low CSF ORX levels during the hypersomnia episodes [83, 84]. In a sample of 24 patients, lower values of BP and HR were found together with lower ORX levels during the symptomatic phase of the syndrome compared with the remission phase [84]. As in IH, the causal role of excessive sleep length and relative inactivity deserves to be investigated. Sleep and inactivity *per se* could potentially lower HR and BP. Thus, the observed autonomic dysfunction would not be linked to the disorder itself, but to the state, e.g. hypersomnia and "bed rest" condition it causes. This hypothesis however needs to be proven.

Medications

Medications for CDH may have potential negative effects on cardiovascular health, especially in NT1, as patients need a life-long treatment [85, 86]. However long-term data on cardiovascular outcomes in these populations are still lacking [23]. Among wake-promoting agents (WPA), modafinil, armodafinil, solriamfetol, methylphenidate and amphetamines have a well-known effect on BP and HR, and the dose level may influence the level of cardiovascular risk [23]. Methylphenidate and amphetamines especially can increase BP, HR, and induce cardiac arrhythmias. An important study (already mentioned above) with 160 NT1 patients showed that patients treated with stimulants had higher 24h, daytime, and nighttime diastolic BP or HR compared with untreated patients. Hypertension was diagnosed in 58% of treated patients versus 41% of untreated patients [87]. A recent study showed that solriamfetol was associated with small mean increases in HR and systolic and diastolic BP at doses of 150 and 300 mg/d in narcolepsy [88]. Pitolisant is different than other WPA, as it has a histaminergic mechanism of action. It was associated with slight QT interval prolongation but without clinically meaningful cardiovascular changes [89]. Antidepressant agents are widely used (off-label) to treat cataplexy, and may also have an impact on the autonomic nervous system. At last, sodium oxybate (the sodium salt of gamma-hydroxybutyrate) can improve all narcolepsy symptoms (sleepiness, cataplexy, DNS). Sodium intake is known to increase BP and cardiovascular risk, this treatment should thus be used with caution. Recently, a lower-sodium oxybate (calcium, magnesium, potassium, and sodium oxybate) was developed to treat

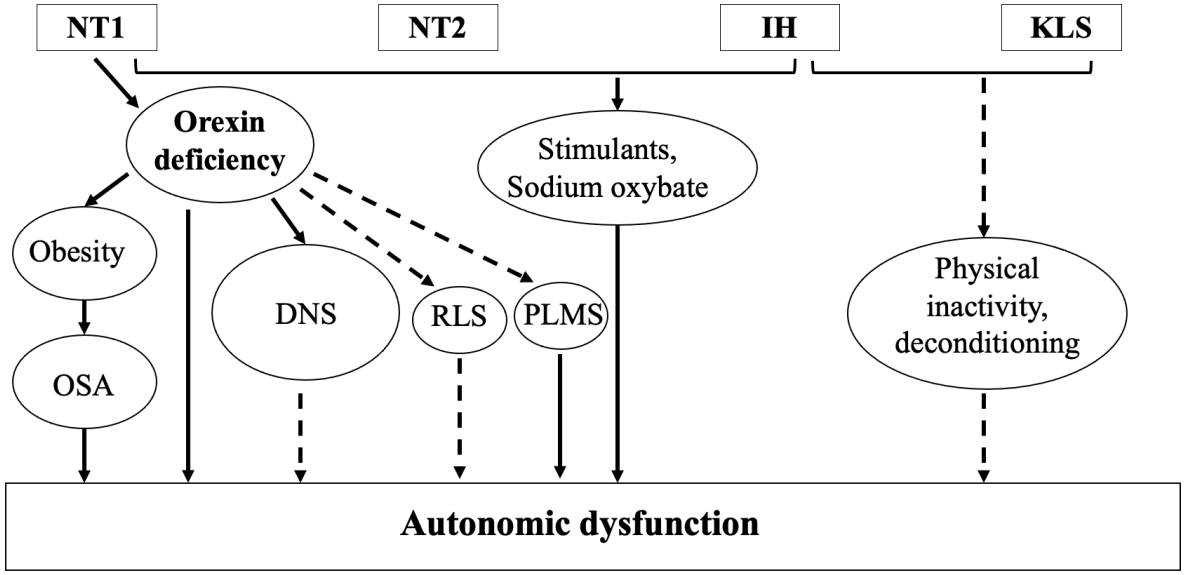
narcolepsy, and also idiopathic hypersomnia [90, 91]. The effect on sleepiness, symptoms severity and self-reported patient global impression of change were shown in a placebo-controlled double-blind randomized withdrawal study in patients with idiopathic hypersomnia.

Conclusions

The recent integration of data from multiple approaches, including preclinical studies, and clinical research, has increased our understanding of the complex relationships between autonomic nervous system and CDH. Autonomic disturbances in narcolepsy have been well explored, but findings remain hard to generalize, because different populations were involved, various methods were used, and results were obtained in different conditions (sleep or wakefulness). Also, the impact of autonomic alterations on medical outcomes, life expectancy in narcolepsy remains unknown. Sleepiness is a common symptom in the general population and hypersomnolence is an active area of research, with several new wake-promoting agents developed over the past years [85]. The upcoming arrival of non-peptide agonists of ORX receptor 2 to manage narcolepsy also offers new perspectives in the field [92]. The effect of these drugs on the autonomic nervous system should be systematically evaluated in future studies, especially on cardiovascular parameters. A 24-hour BP monitoring seems mandatory in future clinical trials. The pathophysiology of autonomic dysfunction in CDH and its possible relation to cardiovascular risk need to be further explored, with large systematic assessment and careful follow-up of homogeneous groups of well-characterized patients.

Figure. Schematic representation of mechanisms of autonomic dysfunction in central disorders of hypersomnolence. Full-line arrows represent well-documented associations, mostly in narcolepsy type 1, whereas dotted arrows represent putative mechanisms. The relative implication of each factor is quantified in the table below (+++ strong, ++ moderate, + mild, - absent,? unknown).

Abbreviations: DNS: disrupted nocturnal sleep; IH: idiopathic hypersomnia; KLS: Kleine-Levin syndrome; NT1: narcolepsy type 1; NT2: narcolepsy type 2; OSA: obstructive sleep apnea; PLMS: periodic limbs movements; RLS: restless legs syndrome



	NT1	NT2	IH	KLS
Orexin deficiency	+++	+/?	-	↑↓
Obesity	+++			
OSA	++	+		
DNS	+++	+	-	
Stimulants	+++	+++	+++	
Sodium oxybate	+	+	+	
RLS	+	+		
PLMS	++	+		
Physical inactivity			++	++

Disclosure.

Alessandro Silvani is an inventor in Italian patent application n. 102022000013894 related to a novel dual orexin receptor agonist and received speaker fees by Idorsia. Isabelle Lambert declares that she has no conflict of interest related to this article. Anna Heidbreder declares that she has no conflict of interest related to this article. Yves Dauvilliers declares that he has no conflict of interest related to this article; he received funds for seminars, board engagements and travel to conferences by UCB Pharma, Jazz, Theranexus, Idorsia, Takeda, Avadel and

Bioprojet. Lucie Barateau declares that she has no conflict of interest related to this article; she received funds for traveling to conferences by UCB Pharma, Idorsia, and Bioprojet, and board engagements by Jazz, Takeda, Idorsia and Bioprojet.

Human and Animal Rights.

All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

REFERENCES

Original papers of particular interest for the topic have been highlighted as:
* Of importance

1. Calandra-Buonaura G, Provini F, Guaraldi P, Plazzi G, Cortelli P (2016) Cardiovascular autonomic dysfunctions and sleep disorders. Sleep Medicine Reviews 26:43–56
2. AASM: American Academy of Sleep Medicine (2014) ICSD-3: International Classification of Sleep Disorders, 3rd ed. American Academy of Sleep Medicine.
3. Dauvilliers Y, Barateau L (2017) Narcolepsy and Other Central Hypersomnias. Continuum (Minneap Minn) 23:989–1004
4. Lammers GJ, Bassetti CLA, Dolenc-Groselj L, et al (2020) Diagnosis of central disorders of hypersomnolence: A reappraisal by European experts. Sleep Med Rev 52:101306
5. Dauvilliers Y, Barateau L, Lopez R, Rassu AL, Chenini S, Beziat S, Jaussent I (2020) Narcolepsy Severity Scale: A reliable tool assessing symptom severity and consequences. Sleep. https://doi.org/10.1093/sleep/zsaa009
6. Barateau L, Lopez R, Chenini S, Rassu AL, Mouhli L, Dhalluin C, Jaussent I, Dauvilliers Y (2022) Linking clinical complaints and objective measures of Disrupted Nighttime Sleep in Narcolepsy type 1. Sleep zsac054
7. Bassetti CLA, Adamantidis A, Burdakov D, et al (2019) Narcolepsy - clinical spectrum, aetiopathophysiology, diagnosis and treatment. Nat Rev Neurol 15:519–539
8. Barateau L, Pizza F, Plazzi G, Dauvilliers Y (2022) Narcolepsy. J Sleep Res e13631
9. Peyron C, Tighe DK, van den Pol AN, de Lecea L, Heller HC, Sutcliffe JG, Kilduff TS (1998) Neurons containing hypocretin (orexin) project to multiple neuronal systems. J Neurosci 18:9996–10015
10. Pizza F, Barateau L, Dauvilliers Y, Plazzi G (2022) The orexin story, sleep and sleep disturbances. J Sleep Res 31:e13665
* 11. Bastianini S, Silvani A, Berteotti C, Elghozi J-L, Franzini C, Lenzi P, Lo Martire V, Zoccoli G (2011) Sleep related changes in blood pressure in hypocretin-deficient narcoleptic mice. Sleep 34:213–218
[The first published evidence that lack of orexins attenuates differences in blood pressure between sleep and wakefulness.
12. Alvente S, Berteotti C, Bastianini S, Lo Martire V, Matteoli G, Silvani A, Zoccoli G (2021) Autonomic Mechanisms Of Blood Pressure Alterations During Sleep In Orexin/Hypocretin-Deficient Narcoleptic Mice. Sleep. https://doi.org/10.1093/sleep/zsab022
13. Barateau L, Lopez R, Dauvilliers Y (2016) Treatment Options for Narcolepsy. CNS Drugs 30:369–379
14. Plazzi G, Moghadam KK, Maggi LS, et al (2011) Autonomic disturbances in narcolepsy. Sleep Med Rev 15:187–196
* 15. Barateau L, Chenini S, Evangelista E, Jaussent I, Lopez R, Dauvilliers Y (2019) Clinical autonomic dysfunction in Narcolepsy Type 1. Sleep. https://doi.org/10.1093/sleep/zsz187
[This study demonstrated clinical autonomic dysfunction in NT1 using the validated SCOPA-AUT questionnaire]
16. Miglis MG (2016) Autonomic dysfunction in primary sleep disorders. Sleep Med 19:40–49
17. Rocchi C, Placidi F, Del Bianco C, Liguori C, Pisani A, Mercuri NB, Izzi F (2020) Autonomic symptoms, cardiovascular and sudomotor evaluation in de novo type 1

narcolepsy. Clin Auton Res. https://doi.org/10.1007/s10286-020-00718-w
18. Berteotti C, Silvani A (2017) The link between narcolepsy and autonomic cardiovascular dysfunction: a translational perspective. Clin Auton Res. https://doi.org/10.1007/s10286-017-0473-z
* 19. Dauvilliers Y, Jaussent I, Krams B, Scholz S, Lado S, Levy P, Pepin JL (2012) Non-dipping blood pressure profile in narcolepsy with cataplexy. PLoS ONE 7:e38977
[This study, together with ref. 20 below, was the first to translate to adult patients with NT1 the sleep-related cardiovascular alteration previously obtained in animal models of orexin deficiency (cf. ref. 11)].
* 20. Grimaldi D, Calandra-Buonaura G, Provini F, Agati P, Pierangeli G, Franceschini C, Barletta G, Plazzi G, Montagna P, Cortelli P (2012) Abnormal sleep-cardiovascular system interaction in narcolepsy with cataplexy: effects of hypocretin deficiency in humans. Sleep 35:519–528
[This study, together with ref. 19 above, was the first to translate to adult patients with NT1 the sleep-related cardiovascular alteration previously discovered in animal models of orexin deficiency (cf. ref. 11)].
21. Sieminski M, Partinen M (2016) "Non-dipping" is equally frequent in narcoleptic patients and in patients with insomnia. Sleep Biol Rhythms 14:31–36
22. Ohayon MM (2013) Narcolepsy is complicated by high medical and psychiatric comorbidities: a comparison with the general population. Sleep Med 14:488–492
23. Jennum PJ, Plazzi G, Silvani A, Surkin LA, Dauvilliers Y (2021) Cardiovascular Disorders in Narcolepsy: Review of Associations and Determinants. Sleep Medicine Reviews 101440
* 24. Vandi S, Rodolfi S, Pizza F, Moresco M, Antelmi E, Ferri R, Mignot E, Plazzi G, Silvani A (2019) Cardiovascular autonomic dysfunction, altered sleep architecture, and muscle overactivity during nocturnal sleep in pediatric patients with narcolepsy type 1. Sleep. https://doi.org/10.1093/sleep/zsz169
[This study demonstrated that sleep-related cardiovascular alterations previously discovered in animal models of orexin deficiency (cf. ref. 11) and translated to adult patients with NT1 (cf. refs. 19 and 20) are already detectable in pediatric patients with NT1].
* 25. Donadio V, Liguori R, Vandi S, Giannoccaro MP, Pizza F, Leta V, Plazzi G (2014) Sympathetic and cardiovascular changes during sleep in narcolepsy with cataplexy patients. Sleep Med 15:315–321
[This study measured muscle sympathetic nerve activity together with blood pressure and heart rate during sleep in adult patients with NT1].
26. Sieminski M, Chwojnicki K, Sarkanen T, Partinen M (2017) The relationship between orexin levels and blood pressure changes in patients with narcolepsy. PLoS ONE 12:e0185975
* 27. Bosco A, Lopez R, Barateau L, Chenini S, Pesenti C, Pépin J-L, Jaussent I, Dauvilliers Y (2018) Effect of psychostimulants on blood pressure profile and endothelial function in narcolepsy. Neurology 10–1212
[This study revealed that pharmacological therapy may adversely impact on blood pressure control in adult patients with NT1].
28. Silvani A, Bastianini S, Berteotti C, Lo Martire V, Zoccoli G (2012) Control of cardiovascular variability during undisturbed wake-sleep behavior in hypocretin-deficient mice. Am J Physiol Regul Integr Comp Physiol 302:R958-964
29. Ferini-Strambi L, Spera A, Oldani A, Zucconi M, Bianchi A, Cerutti S, Smirne S (1997) Autonomic function in narcolepsy: power spectrum analysis of heart rate variability. J Neurol 244:252–255
30. Fronczek R, Overeem S, Reijntjes R, Lammers GJ, van Dijk JG, Pijl H (2008)

Increased heart rate variability but normal resting metabolic rate in hypocretin/orexin-deficient human narcolepsy. J Clin Sleep Med 4:248–254
31. Silvani A, Grimaldi D, Barletta G, Bastianini S, Vandi S, Pierangeli G, Plazzi G, Cortelli P (2013) Cardiovascular variability as a function of sleep-wake behaviour in narcolepsy with cataplexy. J Sleep Res 22:178–184
32. Fronczek R, Overeem S, Reijntjes R, Lammers GJ, van Dijk JG, Pijl H (2008) Increased heart rate variability but normal resting metabolic rate in hypocretin/orexin-deficient human narcolepsy. J Clin Sleep Med 4:248–254
33. Antelmi E, Plazzi G, Pizza F, Vandi S, Aricò D, Ferri R (2018) Impact of acute administration of sodium oxybate on heart rate variability in children with type 1 narcolepsy. Sleep Med 47:1–6
34. Donadio V, Liguori R, Vandi S, Pizza F, Dauvilliers Y, Leta V, Giannoccaro MP, Baruzzi A, Plazzi G (2014) Lower wake resting sympathetic and cardiovascular activities in narcolepsy with cataplexy. Neurology 83:1080–1086
* 35. Sorensen GL, Knudsen S, Petersen ER, Kempfner J, Gammeltoft S, Sorensen HBD, Jennum P (2013) Attenuated heart rate response is associated with hypocretin deficiency in patients with narcolepsy. Sleep 36:91–98
[This study found evidence of blunted changes in heart rate associated with sleep microstructural events in adult patients with NT1, in line with results from Ref. 37]
36. van der Meijden WP, Fronczek R, Reijntjes RHAM, Corssmit EPM, Biermasz NR, Lammers GJ, van Dijk JG, Thijs RD (2015) Time- and state-dependent analysis of autonomic control in narcolepsy: higher heart rate with normal heart rate variability independent of sleep fragmentation. J Sleep Res 24:206–214
* 37. Dauvilliers Y, Pennestri M-H, Whittom S, Lanfranchi PA, Montplaisir JY (2011) Autonomic response to periodic leg movements during sleep in narcolepsy-cataplexy. Sleep 34:219–223
[This study found evidence of blunted changes in heart rate associated with periodic leg movements during sleep in adult patients with NT1, in line with results from Ref. 35].
38. de Zambotti M, Pizza F, Covassin N, Vandi S, Cellini N, Stegagno L, Plazzi G (2014) Facing emotions in narcolepsy with cataplexy: haemodynamic and behavioural responses during emotional stimulation. J Sleep Res 23:432–440
39. Grimaldi D, Pierangeli G, Barletta G, Terlizzi R, Plazzi G, Cevoli S, Franceschini C, Montagna P, Cortelli P (2010) Spectral analysis of heart rate variability reveals an enhanced sympathetic activity in narcolepsy with cataplexy. Clinical Neurophysiology 121:1142–1147
40. Martelli D, Silvani A, McAllen RM, May CN, Ramchandra R (2014) The low frequency power of heart rate variability is neither a measure of cardiac sympathetic tone nor of baroreflex sensitivity. Am J Physiol Heart Circ Physiol 307:H1005-1012
41. Grassi G, Seravalle G, Cattaneo BM, Bolla GB, Lanfranchi A, Colombo M, Giannattasio C, Brunani A, Cavagnini F, Mancia G (1995) Sympathetic activation in obese normotensive subjects. Hypertension 25:560–563
42. Kok SW, Overeem S, Visscher TLS, Lammers GJ, Seidell JC, Pijl H, Meinders AE (2003) Hypocretin deficiency in narcoleptic humans is associated with abdominal obesity. Obes Res 11:1147–1154
43. Kotagal S, Krahn LE, Slocumb N (2004) A putative link between childhood narcolepsy and obesity. Sleep Med 5:147–150
* 44. Schuld A, Hebebrand J, Geller F, Pollmächer T (2000) Increased body-mass index in patients with narcolepsy. Lancet 355:1274–1275
[This study provided one of the first demonstrations of metabolic alterations associated with NT1]
* 45. Dauvilliers Y, Barateau L, Middleton B, van der Veen DR, Skene DJ (2022)

Metabolomics Signature of Patients With Narcolepsy. Neurology 98:e493–e505
[This study provided an in-depth view of the metabolic changes associated with NT1 taking advantage of cutting-edge metabolomics]
46. Chabas D, Foulon C, Gonzalez J, Nasr M, Lyon-Caen O, Willer J-C, Derenne J-P, Arnulf I (2007) Eating disorder and metabolism in narcoleptic patients. Sleep 30:1267–1273
47. Dahmen N, Tonn P, Messroghli L, Ghezel-Ahmadi D, Engel A (2009) Basal metabolic rate in narcoleptic patients. Sleep 32:962–964
48. Kreier F, Fliers E, Voshol PJ, et al (2002) Selective parasympathetic innervation of subcutaneous and intra-abdominal fat--functional implications. J Clin Invest 110:1243–1250
49. Enevoldsen LH, Tindborg M, Hovmand NL, Christoffersen C, Ellingsgaard H, Suetta C, Stallknecht BM, Jennum PJ, Kjær A, Gammeltoft S (2018) Functional brown adipose tissue and sympathetic activity after cold exposure in humans with type 1 narcolepsy. Sleep 41:zsy092
50. Sansa G, Iranzo A, Santamaria J (2010) Obstructive sleep apnea in narcolepsy. Sleep Med 11:93–95
51. Maski K, Mignot E, Plazzi G, Dauvilliers Y (2021) Disrupted nighttime sleep and sleep instability in narcolepsy. J Clin Sleep Med. https://doi.org/10.5664/jcsm.9638
*52. McAlpine CS, Kiss MG, Rattik S, et al (2019) Sleep modulates haematopoiesis and protects against atherosclerosis. Nature 566:383–387
[This study on animal models provided the first evidence of a link between orexin deficiency and increased atherosclerosis burden]
53. Dauvilliers Y, Beziat S, Pesenti C, et al (2017) Measurement of narcolepsy symptoms The Narcolepsy Severity Scale. Neurology 88:1358–1365
54. Plazzi G, Ferri R, Antelmi E, et al (2010) Restless legs syndrome is frequent in narcolepsy with cataplexy patients. Sleep 33:689–694
55. Dauvilliers Y, Pennestri M-H, Petit D, Dang-Vu T, Lavigne G, Montplaisir J (2007) Periodic leg movements during sleep and wakefulness in narcolepsy. J Sleep Res 16:333–339
56. Plazzi G, Ferri R, Franceschini C, Vandi S, Detto S, Pizza F, Poli F, De Cock VC, Bayard S, Dauvilliers Y (2012) Periodic leg movements during sleep in narcoleptic patients with or without restless legs syndrome. J Sleep Res 21:155–162
57. Dauvilliers Y, Jennum P, Plazzi G (2013) Rapid eye movement sleep behavior disorder and rapid eye movement sleep without atonia in narcolepsy. Sleep Med 14:775–781
*58. Barateau L, Jaussent I, Lopez R, Evangelista E, Chenini S, Benkiran M, Mariano-Goulart D, Dauvilliers Y (2018) Cardiac sympathetic activity differentiates Idiopathic and symptomatic Rapid Eye Movement Sleep disorder. Sci Rep. 2018 May 8;8(1):7304.
[This study found a difference in cardiac scintigraphy between patients with NT1 and RBD and patients with idiopathic RBD, supporting different processes involved in RBD pathogenesis]
*59. Barateau L, Lopez R, Chenini S, Evangelista E, Benkiran M, Mariano-Goulart D, Jaussent I, Dauvilliers Y (2019) Exploration of cardiac sympathetic adrenergic nerve activity in narcolepsy. Clin Neurophysiol 130:412–418
[This study found evidence of normal cardiac sympathetic innervation in NT1].
60. Clark RW, Boudoulas H, Schaal SF, Schmidt HS (1980) Adrenergic hyperactivity and cardiac abnormality in primary disorders of sleep. Neurology 30:113–119
61. Yoss RE, Moyer NJ, Ogle KN (1969) The pupillogram and narcolepsy. A method to measure decreased levels of wakefulness. Neurology 19:921–928
62. Karacan I (1986) Erectile dysfunction in narcoleptic patients. Sleep 9:227–231
63. Wang J, Yan Z, Dong X, Li J, Zhao L, Zhang X, Lv C, Zhao Z, Strohl KP, Han F (2022) Diurnal changes in blood pressure and heart rate in children with narcolepsy with cataplexy. J Sleep Res e13736

*64. Jagadish S, Singer W, Kotagal S (2021) Autonomic dysfunction in childhood hypersomnia disorders. Sleep Med 78:43–48
[This study reported a high prevalence of orthostatic hypotension in pediatric patients with hypersomnia disorders]
65. Baumann-Vogel H, Schreckenbauer L, Valko PO, Werth E, Baumann CR (2020) Narcolepsy type 2: A rare, yet existing entity. J Sleep Res e13203
66. Barateau L, Lopez R, Chenini S, Rassu A-L, Scholz S, Lotierzo M, Cristol J-P, Jaussent I, Dauvilliers Y (2020) Association of CSF Orexin-A levels and nocturnal sleep stability in patients with hypersomnolence. Neurology. https://doi.org/10.1212/WNL.0000000000010743
67. Lopez R, Barateau L, Rassu AL, Evangelista E, Chenini S, Scholz S, Jaussent I, Dauvilliers Y (2022) Rapid eye movement sleep duration during the multiple sleep latency test to diagnose hypocretin-deficient narcolepsy. Sleep zsac247
68. Aslan S, Erbil N, Tezer FI (2018) Heart Rate Variability During Nocturnal Sleep and Daytime Naps in Patients With Narcolepsy Type 1 and Type 2. J Clin Neurophysiol. https://doi.org/10.1097/WNP.0000000000000544
69. Dauvilliers Y, Bogan RK, Arnulf I, Scammell TE, St Louis EK, Thorpy MJ (2022) Clinical considerations for the diagnosis of idiopathic hypersomnia. Sleep Med Rev 66:101709
70. Evangelista E, Lopez R, Barateau L, Chenini S, Bosco A, Jaussent I, Dauvilliers Y (2018) Alternative diagnostic criteria for idiopathic hypersomnia: A 32-hour protocol. Ann Neurol 83:235–247
71. Lopez R, Doukkali A, Barateau L, Evangelista E, Chenini S, Jaussent I, Dauvilliers Y (2017) Test–Retest Reliability of the Multiple Sleep Latency Test in Central Disorders of Hypersomnolence. Sleep 40:zsx164
72. Adra N, Reddy M, Attarian H, Sahni AS (2022) Autonomic dysfunction in idiopathic hypersomnia: an overlooked association and potential management. J Clin Sleep Med 18:963–965
73. Bassetti C, Aldrich MS (1997) Idiopathic hypersomnia. A series of 42 patients. Brain 120 (Pt 8):1423–1435
74. Vernet C, Leu-Semenescu S, Buzare M-A, Arnulf I (2010) Subjective symptoms in idiopathic hypersomnia: beyond excessive sleepiness. J Sleep Res 19:525–534
75. Baker TL, Guilleminault C, Nino-Murcia G, Dement WC (1986) Comparative polysomnographic study of narcolepsy and idiopathic central nervous system hypersomnia. Sleep 9:232–242
76. Sforza E, Roche F, Barthélémy JC, Pichot V (2016) Diurnal and nocturnal cardiovascular variability and heart rate arousal response in idiopathic hypersomnia. Sleep Med 24:131–136
77. AASM: American Academy of Sleep Medicine (2014) ICSD-3: International Classification of Sleep Disorders, 3rd ed. American Academy of Sleep Medicine.
*78. Miglis MG, Schneider L, Kim P, Cheung J, Trotti LM (2020) Frequency and severity of autonomic symptoms in idiopathic hypersomnia. J Clin Sleep Med 16:749–756
[This study reported that symptoms of autonomic nervous system dysfunction, as assessed with the COMPASS-31 score, are common in patients with idiopathic hypersomnia].
79. Parsaik A, Allison TG, Singer W, Sletten DM, Joyner MJ, Benarroch EE, Low PA, Sandroni P (2012) Deconditioning in patients with orthostatic intolerance. Neurology 79:1435–1439
80. Arnulf I, Rico TJ, Mignot E (2012) Diagnosis, disease course, and management of patients with Kleine-Levin syndrome. Lancet Neurol 11:918–928
81. Dauvilliers Y, Mayer G, Lecendreux M, Neidhart E, Peraita-Adrados R, Sonka K,

Billiard M, Tafti M (2002) Kleine-Levin syndrome: an autoimmune hypothesis based on clinical and genetic analyses. Neurology 59:1739–1745
82. Ambati A, Hillary R, Leu-Semenescu S, et al (2021) Kleine-Levin syndrome is associated with birth difficulties and genetic variants in the TRANK1 gene loci. Proc Natl Acad Sci U S A 118:e2005753118
83. Lopez R, Barateau L, Chenini S, Dauvilliers Y (2015) Preliminary results on CSF biomarkers for hypothalamic dysfunction in Kleine-Levin syndrome. Sleep Med 16:194–196
*84. Wang JY, Han F, Dong SX, et al (2016) Cerebrospinal Fluid Orexin A Levels and Autonomic Function in Kleine-Levin Syndrome. Sleep 39:855–860
[This study found lower orexin A levels in the cerebrospinal fluid in the symptomatic phase of the Kleine-Levin syndrome than in remission]
85. Barateau L, Dauvilliers Y (2019) Recent advances in treatment for narcolepsy. Ther Adv Neurol Disord 12:1756286419875622
86. Barateau L, Dauvilliers Y (2021) Hypersomnias of Central Origin. Treatment. Sleep Medicine Textbook, European Sleep Research Society
*87. Bosco A, Lopez R, Barateau L, Chenini S, Pesenti C, Pépin J-L, Jaussent I, Dauvilliers Y (2018) Effect of psychostimulants on blood pressure profile and endothelial function in narcolepsy. Neurology 90:e479–e491
88. Thorpy MJ, Shapiro C, Mayer G, et al (2019) A randomized study of solriamfetol for excessive sleepiness in narcolepsy. Ann Neurol 85:359–370
89. Dauvilliers Y, Arnulf I, Szakacs Z, Leu-Semenescu S, Lecomte I, Scart-Gres C, Lecomte J-M, Schwartz J-C, HARMONY III study group (2019) Long-term use of pitolisant to treat patients with narcolepsy: Harmony III Study. Sleep. https://doi.org/10.1093/sleep/zsz174
90. Bogan RK, Thorpy MJ, Dauvilliers Y, Partinen M, Del Rio Villegas R, Foldvary-Schaefer N, Skowronski R, Tang L, Skobieranda F, Šonka K (2020) Efficacy and safety of calcium, magnesium, potassium, and sodium oxybates (lower-sodium oxybate [LXB]; JZP-258) in a placebo-controlled, double-blind, randomized withdrawal study in adults with narcolepsy with cataplexy. Sleep. https://doi.org/10.1093/sleep/zsaa206
91. Dauvilliers Y, Arnulf I, Foldvary-Schaefer N, et al (2022) Safety and efficacy of lower-sodium oxybate in adults with idiopathic hypersomnia: a phase 3, placebo-controlled, double-blind, randomised withdrawal study. Lancet Neurol 21:53–65
92. Evans R, Kimura H, Alexander R, et al (2022) Orexin 2 receptor-selective agonist danavorexton improves narcolepsy phenotype in a mouse model and in human patients. Proc Natl Acad Sci U S A 119:e2207531119